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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07C 237/22, A61K 31/16 — A1

(11) International Publication Number: WO 93/15045

(43) International Publication Date: 5 August 1993 (05.08.93)

(21) International Application Number: PCT/US93/00557

(22) International Filing Date: 19 January 1993 (19.01.93)

(30) Priority data:
07/827,244 29 January 1992 (29.01.92) US
07/968,636 29 October 1992 (29.10.92) US

(60) Parent Applications or Grants
(63) Related by Continuation
US 07/827,244 (CIP)
Filed on 29 January 1992 (29.01.92)
US 07/968,636 (CIP)
Filed on 29 October 1992 (29.10.92)

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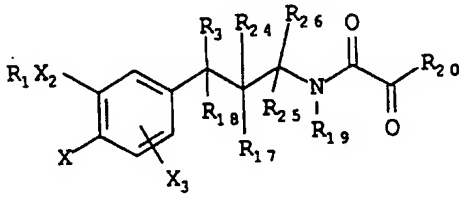
(81) Designated States: AU, CA, JP, KR, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: N-(3-PHENYLPROPYL)OXAMIC ACID, OXAMATE, AND OXAMIDE DERIVATIVES



(I)

(57) Abstract

Novel oxamides of formula (I) which inhibit PDE IV and TNF are described herein.

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Field of Invention

The present invention relates to novel oxamides, pharmaceutical compositions containing these compounds and their use in treating allergic and inflammatory diseases and for inhibiting the production of Tumor Necrosis Factor (TNF).

Background of the Invention

Bronchial asthma is a complex, multifactorial disease characterized by reversible narrowing of the airway and hyperactivity of the respiratory tract to external stimuli.

It is now understood that the symptoms of chronic asthma are the manifestations of three distinct processes: 1) an early response to antigen, 2) a delayed or late response to antigen, and 3) chronic inflammation and airway hyperactivity. Cockcroft, Ann. Allergy 55:857-862, 1985; Larsen, Hosp. Practice 22:113-127, 1987.

The agents currently available (β-adrenoceptor agonists, steroids, methylxanthines, disodium cromoglycate) are inadequate to control the disease; none of them modify all three phases of asthma and nearly all are saddled with limiting side effects. Most importantly, none of the agents, with the possible exception of steroids, alter the course of progression of chronic asthma.

Cyclic AMP modulates the activity of most, if not all, of the cells that contribute to the pathophysiology of extrinsic (allergic) asthma. As such, an elevation of cAMP would produce beneficial effects including: 1) airway sooth muscle relaxation, 2) inhibition of mast cell mediator release, 3) suppression of neutrophil degranulation, 4) inhibition of basophil degranulation, and 5) inhibition of monocyte and macrophage activation. Hence, compounds that activate adenylate cyclase or inhibit PDE should be effective in suppressing the inappropriate activation of airway smooth muscle and a wide variety of inflammatory cells. The principal cellular mechanism for the inactivation of cAMP is hydrolysis of the 3'-phosphodiester bond by one or more of a family of isozymes referred to as cyclic nucleotide phosphodiesterases (PDEs).

It has now been shown that a distinct cyclic nucleotide phosphodiesterase (PDE) isozyme, PDE IV, is responsible for cyclic AMP breakdown in airway smooth muscle and inflammatory cells. Torphy, "Phosphodiesterase Isozymes: Potential Targets for Novel Anti-asthmatic Agents" in New Drugs for Asthma, Barnes, ed. IBC Technical Services Ltd. (1989). Research indicates that inhibition of this enzyme not only produces airway smooth muscle relaxation, but also suppresses degranulation of mast cells, basophils and neutrophils along with inhibiting the activation of monocytes and neutrophils. Moreover, the beneficial effects of PDE IV inhibitors are markedly potentiated when adenylate cyclase activity of target cells is elevated by appropriate hormones or autocoids, as would be the case in vivo. Thus PDE IV inhibitors would be effective in the asthmatic lung, where levels of prostaglandin E_2 and prostacyclin (activators of adenylate cyclase) are elevated. Such

compounds would offer a unique approach toward the pharmacotherapy of bronchial asthma and possess significant therapeutic advantages over agents currently on the market.

The compounds of this invention also inhibit production of Tumor Necrosis Factor (TNF), a serum glycoprotein. Excessive or unregulated TNF production is implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sacroidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

TNF has been implicated in various roles with the human acquired immune deficiency syndrome (AIDS). AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). It has now been discovered that monokines, specifically TNF, are implicated in the infection of T lymphocytes with HIV by playing a role in maintaining T lymphocyte activation. Furthermore, once an activated T lymphocytes is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. It has also been discovered that monokines, specifically TNF, are implicated in activated T cell-mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with monokine activity such as by ihibition of monokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg et al., The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, (1989)]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli, et al., Proc. Natl. Acad. Sci., 87:782-784 (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T cells.

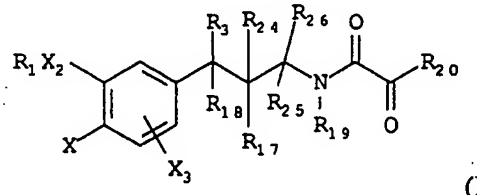
It has now been discovered that monokines are implicated in certain disease-associated problems such as cachexia and muscle degeneration. Therefore, interference with monokine activity, such as by inhibition of TNF production, in an HIV-infected individual aids in enhancing the quality of life of HIV-infected patients by reducing the severity of monokine-mediated disease associated problems such as cachexia and muscle degeneration.

TNF is also associated with yeast and fungal infections. Specifically Candida Albicans has been shown to induce TNF production in vitro in human monocytes and natural killer cells. [See Riipi et al., Infection and Immunity, Vol. 58, No. 9, p. 2750-54 (1990); and Jafari et al., Journal of Infectious Diseases, Vol. 164, p. 389-95 (1991). See also Wasan et al., Antimicrobial Agents and Chemotherapy, Vol. 35, No. 10, p. 2046-48 (1991) and Luke et al., Journal of Infectious Diseases, Vol. 162, p. 211-214 (1990)].

The discovery of a class of compounds which inhibit the production of TNF will provide a therapeutic approach for the diseases in which excessive, or unregulated TNF production is implicated.

Summary of the Invention

This invention comprises oxamides represented by Formula (I)



(I)

R_1 is C_{1-12} alkyl unsubstituted or substituted by 1 or more halogens, C_{3-6} cyclic alkyl unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group, C_{4-6} cycloalkyl containing one or two unsaturated bonds, C_{7-11} polycycloalkyl, -$(CR_{14}R_{14})_nC(O)$-O-$(CR_{14}R_{14})_m$-R_{10}, -$(CR_{14}R_{14})_nC(O)$-O-$(CR_{14}R_{14})_r$-R_{11}, -$(CR_{14}R_{14})_x$OH, -$(CR_{14}R_{14})_sO(CR_{14}R_{14})_m$-$R_{10}$, -$(CR_{14}R_{14})_sO(CR_{14}R_{14})_r$-$R_{11}$, -$(CR_{14}R_{14})_n$-$(C(O)NR_{14})$-$(CR_{14}R_{14})_m$-$R_{10}$, -$(CR_{14}R_{14})_n$ -$(C(O)NR_{14})$-$(CR_{14}R_{14})_r$-R_{11}, -$(CR_{14}R_{14})_y$-R_{11}, or -$(CR_{14}R_{14})_z$-R_{10};

X is YR_2, halogen, nitro, $NR_{14}R_{14}$, or formamide;

X_2 is O or NR_{14};

X_3 is hydrogen or X;

Y is O or $S(O)_m$;

R_2 is -CH_3 or -CH_2CH_3, each may be unsubstituted or substituted by 1 to 5 fluorines;

R_3 is hydrogen, halogen, CN, C_{1-4}alkyl, halo-substituted C_{1-4}alkyl, cyclopropyl unsubstituted or substituted by R_9, -OR_5, -CH_2OR_5, -NR_5R_{16}, -$CH_2NR_5R_{16}$, -$C(O)OR_5$, -$C(O)NR_5R_{16}$, -$CH{=}CR_9R_9$, -$C{\equiv}CR_9$ or -C(Z)H;

R_4 is independently hydrogen, Br, F, Cl, -NR_5R_{16}, NR_6R_{16}, -NO_2, -$C(Z)R_7$, -$S(O)_mR_{12}$, -CN, OR_5, -$OC(O)NR_5R_{16}$, (1 or 1-(R_5)-2-imidazolyl), -$C(NR_{16})NR_5R_{16}$, -$C(NR_5)SR_{12}$, -$OC(O)R_5$, -$C(NCN)NR_5R_{16}$, -$C(S)NR_5R_{16}$, $N(R_{16})C(O)R_{15}$, oxazolyl, thiazolyl, pyrazolyl, triazolyl or tetrazolyl, or when R_5 and R_{16} are NR_5R_{16} they may

together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S;

R_5 is independently hydrogen or C_{1-4}alkyl, unsubstituted or substituted by one to three fluorines;

R_6 is R_5, $-C(O)R_5$, $-C(O)C(O)R_7$, $-C(O)NR_5R_{16}$, $-S(O)_mR_{12}$, $-C(NCN)SR_{12}$, $-C(NCN)R_{12}$, $-C(NR_{16})R_{12}$, $-C(NR_{16})SR_{12}$, or $-C(NCN)NR_5R_{16}$;

R_7 is OR_5, $-NR_5R_{16}$, or R_{12};

R_8 is hydrogen or A;

R_9 is hydrogen, F or R_{12};

R_{10} is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC_{1-3}alkyl, halo substituted arlyoxyC_{1-3}alkyl, indanyl, indenyl, C_{7-11} polycyclo-alkyl, furanyl, pyranyl, thienyl, thiopyranyl, (3- or 4-tetrahydropyranyl), (3- or 4-tetrahydrothiopyranyl), 3-tetrahydrofuranyl, 3-tetrahydrothienyl, C_{3-6} cylcoalkyl, or a C_{4-6}cycloalkyl containing one or two unsaturated bonds, wherein the cylcoalkyl and heterocyclic moieties may be unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

R_{11} is 2-tetrahydropyranyl or 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl or 2-tetrahydrothienyl unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

R_{12} is C_{1-4}alkyl unsubstituted or substituted by one to three fluorines;

R_{14} is independently hydrogen or a C_{1-2}alkyl unsubstituted or substituted by fluorine;

R_{15} is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, or pyrrolyl, and each of the heterocyclics may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{16} is OR_5 or R_5, or when R_5 and R_{16} are NR_5R_6 they may, together with the nitrogen, form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N, or S;

R_{17} and R_{26} are independently hydrogen, halogen, C_{1-4}alkyl, halo-substituted C_{1-4}alkyl, cyclopropyl unsubstituted or substituted by R_9, $-CH_2OR_5$, $-CH_2NR_5R_{16}$, $-C(O)OR_5$, $-C(O)NR_5R_{16}$ or $-C(Z)H$;

R_{18}, R_{24} and R_{25} are independently hydrogen, F, CN, and C_{1-4} alkyl optionally substituted by one or more fluorines; or

R_3 and R_{18} together can form a (=O) keto or cyclopropyl moiety;

provided that when R_3 is OH then R_{18} is hydrogen or CH_3;

R_{19} is hydrogen, $-(CH_2)_mA$, or $-CH_2O(CH)_mA$;

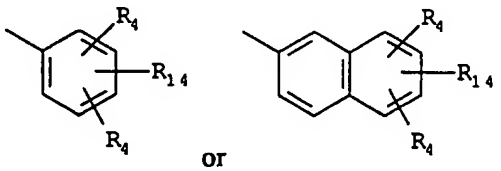
R_{20} is $-O(CH_2)_qR_8$, $-NR_5OR_5$, $-NR_5NR_5R_8$, $-NR_5(CH_2)_qR_8$, $-OCH_2NR_5C(O)R_{21}$, $-OCH_2C(O)NR_{22}R_{23}$, $-OCH(R_5)OC(O)$, C_{1-4}alkyl, $-OCH(R_5)C(O)OC_{1-3}$alkyl;

R_{21} is CH_3 or phenyl;

R_{22} is hydrogen, CH_3, CH_2CH_3, or CH_2CH_2OH;

R_{23} is hydrogen, CH_3, CH_2CH_3, CH_2CH_2OH, or CH_2CONH_2;

A is C_{1-6}alkyl (2-, 3-, or 4-pyridyl), 4-morpholinyl, 4-piperidinyl, (1-, 2-, 4- or 5-imidazolyl), (2- or 3-thienyl), (2- or 5-pyrimidyl), (4 or 5-thiazolyl), triazolyl or quinolinyl, all of which may be unsubstituted or substituted by one or more R_4 groups; or A is $-(CH_2)_rSR_{12}$; or A is a formula of (a) or (b)



(a) or (b)

where the R_4 and R_{14} groups on the naphtyl ring may be substituted at any open position;

Z is O, NR_{12}, NOR_5, NCN, $C(\text{-CN})_2$, CR_5NO_2, $CR_5C(O)OR_5$, $CR_5C(O)NR_5R_5$, -C(-CN)NO_2, $C(\text{-CN})C(O)OR_{12}$ or $C(\text{-CN})C(O)NR_5R_5$;

m is 0 to 2;

n is 1 to 4;

q is 0 to 1;

r is 1 to 2;

s is 2 to 4;

x is 2 to 6;

y is 1 to 6;

z is 0 to 6;

or a pharmaceutically acceptable salt thereof;

provided that:

m is 2 when R_{10} is OH in $(CR_{14}R_{14})_n\text{-}C(O)O\text{-}(CR_{14}R_{14})_m\text{-}R_{10}$, $(CR_{14}R_{14})_n\text{-}(C(O)NR_{14})\text{-}(CR_{14}R_{14})_m\text{-}R_{10}$, or $C(R_{14}R_{14})_sO(CR_{14}R_{14})_mR_{10}$; and further provided that

when A is N-morpholinyl, N-piperidinyl, N-imidazolyl or N-triazolyl, then q is not 1; and

Z is 2-6 in $-C(R_{14}R_{14})_zR_{10}$ when R_{10} is OH.

This invention further comprises a method of inhibiting phosphodiesterase IV in an animal, including humans, which method comprises administering to an animal in need thereof an effective amount of a compound of Formula (I).

This invention further comprises a method of inhibiting the production of TNF in an animal, including humans which method comprises administering to an animal in need thereof an effective amount of a compound of Formula (I).

This invention also relates to a method of treating a human afflicted with a human immunodeficiency virus (HIV), AIDS Related Complex (ARC) or any other disease state associated with an HIV infection, which comprises administering to such a human an effective TNF inhibiting amount of a compound of Formula (I).

The present invention also provides a method of preventing a TNF mediated disease state in an animal in need thereof, including humans, by prophylactically administering an effective amount of a compound of Formula (I).

The compounds of the present invention are also useful in the treatment of additional viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production in vivo. The viruses contemplated for treatment herein are those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (I). Such viruses include, but are not limited to; HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses, such as, Herpes Zoster and Herpes Simplex.

The compounds of Formula (I) are also useful in the treatment of yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production in vivo. A preferred disease state for treatment is fungal meningitis.

Additionally, the compounds of the Formula (I) may be administered in conjunction with other drugs of choice, either simultaneously or in a consecutive manner, for systemic yeast and fungal infections. Drugs of choice for fungal infections, include but are not limited to the class of compounds called the polymixins, such as Polymycin B, the class of compounds called the imidaozles, such as clotrimazole, econazole, miconazole, and ketoconazole; the class of compounds called the triazoles, such as fluconazole, and itranazole, and the class of compound called the Amphotericins, in particular Amphotericin B and liposomal Amphotericin B.

The preferred organism for treatment is the *Candida* organism. The compounds of the Formula (I) may be co-administered in a similar manner with anti-viral or anti-bacterial agents.

The compounds of the Formula (I) may also be used for inhibiting and/or reducing the toxicity of an anti-fungal, anti-bacterial or anti-viral agent by administering an effective amount of a compound of the Formula (I) to a mammal in need of such treatment. Preferably, a compound of the Formula (I) is administered for inhibiting or reducing the toxicity of the Amphotericin class of compounds, in particular Amphotericin B.

Detailed Description of the Invention

All defined alkyl groups can be straight or branched.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are contemplated to be within the scope of the present invention. The term "halogen" is used to mean chloro, fluoro, bromo or iodo. Alkyl groups may be substituted by one or more halogens up to being perhalogenated.

By the term "cycloalkyl" as used herein is meant to include groups of 3-6 carbon atoms, such as cyclopropyl, cyclopropylmethyl, cyclopentyl or cyclohexyl.

By the term "aryl" or "aralkyl", unless specified otherwise, as used herein is meant an aromatic ring or ring system of 6-10 carbon atoms, such as phenyl, benzyl, phenethyl or naphthyl. Preferably the aryl is monocyclic, i.e., phenyl.

Examples of C_{7-11} polycycloalkyl are bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, tricyclo [5.2.1.$0^{2,6}$]decyl, etc., additional examples of which are described in Saccamano et al., WO 87/06576, published 5 November 1987 whose disclosure is incorporated herein by reference in its entirety.

Examples of rings when R_5 and R_{16} in the moiety -NR_5R_{16} together with the nitrogen to which they are attached form a 5- to 7 membered ring optionally containing at least one additional heteroatom selected from O/N/ and S include, but are not limited to 1-imidazolyl, 1-pyrazolyl, 1-triazoly, 2-triazolyl, tetrazolyl, 2-tetrazoyl, morpholinyl, piperazinyl, or pyrrolyl ring.

The term "inhibiting the production of TNF" means:

a) a decrease of excessive in vivo TNF levels in a human to normal levels or below normal levels by inhibition of the in vivo release of TNF by all cells, including but not limited to monocytes or macrophages;

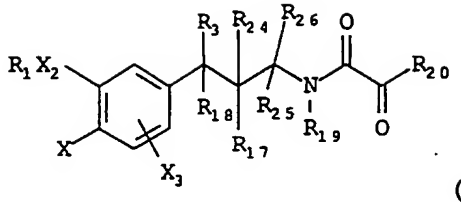
b) a down regulation, at the translational or transcription level, of excessive in vivo TNF levels in a human to normal levels or below normal levels; or

c) a down regulation, by inhibition of the direct synthesis of TNF as a postranslational event.

The term "TNF mediated disease states" means any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released, such as but not limited to IL-1, or IL-6. A disease state in which IL-1, for instance is a major component, and whose production or action is exacerbated or which is secreted in response to TNF, would therefore be considered a disease state mediated by TNF.

The term "cytokine" as used herein means any secreted polypeptide that affects the functions of other cells, and is a molecule which modulates interactions between cells in the immune or inflammatory response. A cytokine includes, but is not limited to monokines and lymphokines regardless of which cells produce them. For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte but many other cells produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes, and β-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines for the present invention include, but are not limited to Interleukin-1 (IL-1), Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNFα) and Tumor Necrosis Factor beta (TNFβ).

A preferred subgroup of Formula (I) is Formula (Ib):



(Ib)

wherein:

R_1 is phenyl, benzyl or C_{1-2} alkyl unsubstituted or substituted by 1 or more fluorines, C_{4-6} cycloalkyl, CH_2-cyclopentyl, CH_2-cyclopropyl, C_{7-11} polycycloalkyl, 3-tetrahydrofuranyl, cyclopentenyl, $-(CH_2)_nC(O)-O-(CH_2)_mCH_3$, $-(CH_2)_{2-4}OH$, $-(CH_2)_sO(CH_2)_m-CH_3$, $-(CH_2)_n-(C(O)NR_{14})-(CH_2)_m-CH_3$, all of which may be unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

s is 2 to 4;

m is 0 to 2;

n is 1 to 3;

X is YR_2, halogen, nitro, amine, C_{1-2}dialkylamine, C_{1-2}monoalkylamine or formamide;

Y is O or $S(O)_m$;

R_2 is $-CH_3$ or $-CH_2CH_3$, each may be unsubstituted or substituted by 1 to 4 fluorines;

R_3 is independently hydrogen, OR_5, F, CF_2H, CH_2F, $-CH_2OR_5$, $C(O)OR_5$, $C(O)NR_5R_5$, C(O)H, $C(NOR_5)H$, CH_3, CN, $-C{\equiv}CR_9$ or CF_3;

A is (2-, 3-, or 4-pyridyl), 4-morpholinyl, 4-piperidinyl, (1- or 2-imidazolyl), (2- or 3-thienyl) or (4- or 5-thiazolyl), all of which may be unsubstituted or substituted by one or more: Br, F, Cl, $-NR_5R_6$, NR_5R_{16}, NR_6R_{16}, NO_2, $-COR_7$, $-S(O)_mR_{12}$, CN, OR_5, $-OC(O)NR_5R_{16}$, (1- or 2-imidazolyl), $-C(NR_{16})NR_5R_{16}$, $-C(NR_5)SR_{12}$, $-OC(O)R_5$, $-C(NCN)NR_5R_{16}$, $-C(S)NR_5R_{16}$, $-NR_{16}C(O)R_{15}$, oxazolyl, thiazolyl, pyrazolyl, triazolyl or tetrazolyl; or when R_5 and R_{16} are as NR_5R_{16} they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S; or A is SR_{12};

R_5 is independently hydrogen or C_{1-4}alkyl, unsubstituted or substituted by one to three fluorines;

R_6 is R_5, $-C(O)R_5$, $-C(O)C(O)R_7$, $-C(O)NR_5R_{16}$, $-S(O)_mR_{12}$, $-C(NCN)SR_{12}$ or $-C(NCN)NR_5R_{16}$;

R_7 is OR_5, NR_5R_{16} or R_5;

R_8 is H or A;

R_9 is R_5;

R_{14} is independently hydrogen or a C_{1-2}alkyl unsubstituted or substituted by fluorine;

R_{15} is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl or pyrrolyl, and each of these heterocyclic rings is connected at a carbon atom and may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{16} is OR_5 or R_5; or a pharmaceutically acceptable salt thereof;

R_{17} and R_{26} are independently hydrogen, halogen, C_{1-4}alkyl, halo-substituted C_{1-4}alkyl, cyclopropyl unsubstituted or substituted by R_9, $-CH_2OR_5$, $-CH_2NR_5R_{16}$, $-C(O)OR_5$, $-C(O)NR_5R_{16}$ or -C(Z)H;

R_{18}, R_{24} and R_{25} are independently H, CN, and C_{1-4} alkyl optionally substituted by one or more fluorines;

R_{19} is hydrogen, $-(CH_2)_mA$, or $-CH_2O(CH_2)_mA$;

R_{20} is $O(CH_2)_qR_8$, $-NR_5OR_5$, $NR_5(CH_2)_qR_8$, $-OCH_2NR_5C(O)R_2$;

R_{21} is CH_3 or phenyl;

R_{22} is hydrogen, CH_3, CH_2CH_3, or CH_2CH_2OH;

R_{23} is hydrogen, CH_3, CH_2CH_3, CH_2CH_2OH, or CH_2CONH_2;

when A is morpholin-4-yl, piperidin-4-yl, imidazol-4-yl, piperidin-4-yl or imidazol-1-yl, then q is not 1.

Preferred compounds are those in which R_1 is CH_2-cyclopropyl, CH_2-C_{5-6} cycloalkyl, C_{4-6} cycloalkyl, phenyl, tetrahydrofuran-3-yl, 3- or 4-cyclopentenyl, $-C_{1-2}$alkyl optionally substituted by one or more fluorines, $-(CH_2)_nC(O)$-O-$(CH_2)_mCH_3$, $-(CH_2)_sO(CH_2)_m$-CH_3 or $-(CH_2)_{2-4}OH$; X_2 is oxygen; X_3 is hydrogen; X is YR_2 and Y is O; R_2 is a C_{1-2}alkyl optionally substituted by one or more fluorines; R_3 is hydrogen, $C{\equiv}CR_9$, CN, C(O)H, CH_2OH, CH_2F, CF_2H, or CF_3; R_{18} is hydrogen, CN or C_{1-4}alkyl optionally substituted by one or more fluorines; R_{19} is hydrogen or $(CH_2)_mA$; R_{20} is $O(CH_2)_qR_8$, NR_5OR_5, or $NR_5(CH_2)_qR_8$.

More preferred are compounds in which R_1 is C_{1-2} alkyl substituted by 1 or more fluorines, CH_2-cyclopropyl, CH_2-cyclopentyl, cyclopentyl or cyclopentenyl; R_2 is methyl or fluoro substituted C_{1-2} alkyl; R_3 is hydrogen, $C{\equiv}CH$ or CN; and A is 2-, 3- or 4-pyridyl, 4-morpholinyl, 2-thienyl, 2-imidazole or 4-thiazolyl, each of which may be substituted or unsubstituted by NR_5R_{16} or $NR_5C(O)R_5$; R_{20} is OR_5, NR_5OR_5 or $NHCH_2A$.

Most preferred are compounds wherein R_1 is cyclopentyl, CF_3, CH_2F, CHF_2, CF_2CHF_2, CH_2CF_3, CH_2CHF_2, CH_3, CH_2-cyclopentyl, CH_2-cyclopropyl or cyclopentenyl; R_2 is CH_3, CF_3, CHF_2, or CH_2CHF_2; one R_3 is hydrogen and the other R_3 is hydrogen, $C{\equiv}CH$ or CN and is in the 4-position.

Especially preferred are the following compounds:

N-[3-(3-cyclopentyloxy-4-methoxyphenyl)propyl]oxamide;

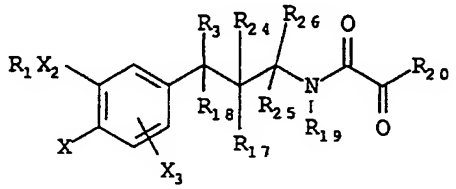
methyl N-[3-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)propyl]oxamate;

N-[3-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-propyl]oxamide; and

N-[3-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-propyl]oxamic acid.

General Synthesis

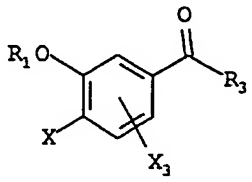
The preparation of the compounds of Formula I(1) can be carried out by one of skill in the art according to the procedures outlined in the Examples, infra. The preparation of any remaining compounds of Formula I(1)



Formula (1)

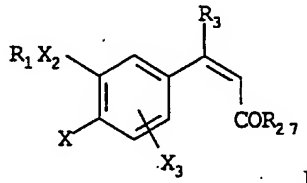
not described therein may be prepared by the analogous processes disclosed herein, which comprises:

a) for compounds wherein R_3 is H, C_{1-2} alkyl optionally substituted by 1 or more fluorines, R_{17}, R_{18}, R_{19}, R_{24}, R_{25} and R_{26} are H, and wherein R_1 represents R_1 as defined in relation to a compound of Formula (I) or a group convertible to R_1 and X and X_3 represents X and X_3 as defined in relation to a compound of Formula (I) or a group convertible to X or X_3, reacting a compound of the Formula (2)



Formula (2)

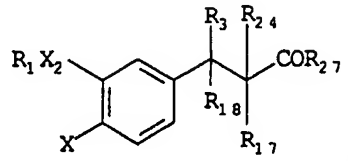
with a malonic acid derivative, such as malonic acid or a malonic acid half ester, in a suitable solvent such as pyridine with (or without) a catalyst at elevated temperatures to provide a compound of the Formula (3), wherein R_{27} is OH, O-alkyl, O-phenyl, or O-benzyl.



Formula (3)

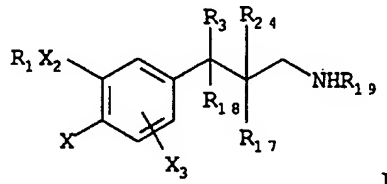
Reduction with a suitable reductant such as hydrogen with a catalyst, except where X or X_3 is SO, SO_2 or NO_2, Br, I and formyl amine; provides a compound of the Formula (4)

wherein R_3, is as defined above for part a), R_{18}, R_{17} and R_{24} are H, and R_{27} is OH, O-alkyl , O-phenyl, or O-benzyl.



Formula (4)

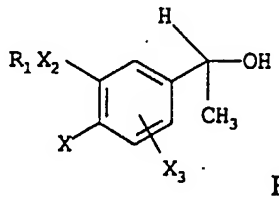
Convering a compound of Formula (4) wherein R_{27} is OH to a compound of Formula (4) wherein R_{27} is NHR_{19} may be accomplished by any of the standard peptide coupling methods well known in the art, e.g. mixed anhydride formation when R_{27} is OH followed by reaction with the amine, NH_2R_{19}. For those compounds in which R_{19} does not possess a reducible functionality, reduction of the amide moiety of a compound of the Formula (4) wherein R_{27} is NHR_{19} provides a compound of the Formula (5) wherein R_3 is as defined above for part a), R_{17} is H and R_{19} is as defined in part in Formula (1)



Formula (5)

Compounds of Formula (5) wherein R_3 is other than $CH_2NR_7R_8$, unless protected by a group such as *t*-butoxycarbonyl or any other easily removed amino protecting groups well known to those skilled in the art, and R_{18} is defined for Formula (1), and R_{19} is H, may be further modified, such as by imine formation with an appropriate aldehyde, followed by reduction, and further modification to produce compounds of Formula (5) wherein R_{19} is other than hydrogen.

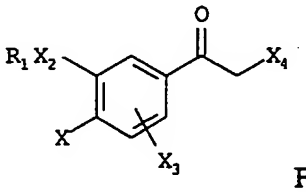
Synthesis of compounds of Formula (1) wherein R_3 is OR_5 or F and R_{18} is H or F, begins by reaction of a compound of Formula (2) wherein R_3 is H with a methyl metal reagent, for example, methyl lithium to provide an alcohol of Formula (2')



Formula (2')

Oxidizing a compound of Formula 2' with an oxidizing agent, for example pyridium dichromate, provides the ketone of Formula (2) as described above wherein R_3 is methyl.

This compound is treated with a halogenating agent, for example copper (II) bromide and heated in a suitable solvent to provide the α-halo ketone of Formula (2") wherein X_4 is a halogen, for example, bromide.



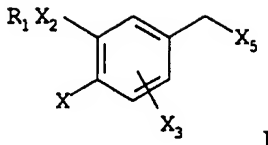
Formula (2")

Displacement of the halogen of Formula (2") by a metal cyanide, such as sodium cyanide, in a suitable solvent, such as dimethylformamide provides, the α-cyanoketone of Formula (2"), wherein X_4 is CN, which is reduced in one or more steps with hydrogen and a catalyst or an appropriate metal hydride to the Formula (5) compound where R3 is OH, and R_{18}, R_{17}, R_{19} and R_{24} are H. For example, treatment of the Formula (2") compound with lithium aluminium hydride to provide the Formula (5) compound. To produce compounds wherein R3 is OR_5 the compounds of Formula (5), wherein R3 is OH and R_{19} is a sutiable amine protecting can be alkylated by treatment with a strong base followed by using alkyl-L, as described above, or by using the process of W. Sheppard, Journal of Organic Chemistry, Vol. 29, page 1-15, (1964).

Treatment of compounds of Formula (1) where R3 is OH, and R_{18}, R_{17} and R_{24} are H with an appropriate oxiziding agent, for example, pyridium dichromate in a suitable solvent, such as DMF provides Formula (1) compounds where R3 and R_{18} together form a keto moiety. Treatment of a Formula (1) compound where R3 is OH or a Formula (5) compound wherein R3 is OH and R_{19} is a removable amine protecting group, such as described in Greene, T., Protective Groups in Organic Synthesis, Wiley Publishers, NY (1981), the contents of which are hereby incorporated by reference; with diethylaminosulfur trifluoride (DAST) provides the corresponding Formula (1) or Formula (5) compounds where R3 or R_{18} is F; which provides the corresponding Formula (1) compounds when treated by any of the methods indicated herein.

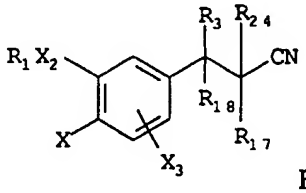
Treatment of Formula (1) or Formula (5) compounds where R3 and R_{18} together form a keto moiety with DAST provides the corresponding Formula (1), or Formula (5) compounds where R3 and R_{18} are both F; which provides the corresponding Formula (1) compounds when treated by any of the methods indicated herein.

Alternatively, synthesis of some compounds of Formula (1) when X or X_3 are other than Br, I, NO_2, or formylamine, begins by reaction of a compound of the Formula (2) with a lithium halide and a silyl halide in an appropriate solvent followed by reduction with an appropriate reductant, such as a siloxane, to provide a compound of Formula (6) wherein X_5 is halogen.



Formula (6)

Halide displacement of a compound of Formula (6) by, e.g., the anion of a cyano acetate, provides the compound of the Formula (7) wherein R_{17} is $COOR_5$ and R_5 is other than H. Ester saponifcation and acid decarboxylation provides a compound of Formula (7), wherein R3, R_{17} and R_{18} are H,

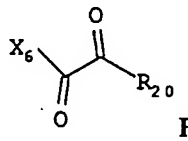


Formula (7)

which is reduced with an appropriate reductant, such as hydrogen with a suitable catalyst, such as nickel with ammonia or palladium on carbon with an acid, such as perchloric acid, to provide a compound of Formula (5), described above, wherein R_{19} is hydrogen.

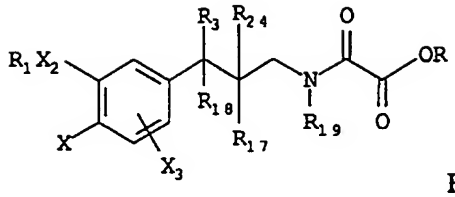
Alternatively, the R_{17} ester group of the above described compounds of Formula (7) may be converted to other compounds of Formula (7) wherein R_{17} is, e.g., $C(O)OR_5$, $C(O)NR_5R_{16}$, C(Z)H, etc., by standard chemical transformation.

Certain compounds of Formula (1) wherein R_{17} is other than $CH_2NR_5R_{16}$ unless suitably protected, are prepared by reacting a compound of Formula (5) with an appropriately activated oxamic acid derivative of a Formula (8) compound wherein X_6 is an activating group, well known to those skilled in the art, such as those disclosed in Bodansky et al., Peptide Synthesis, Wiley & Sons, publishers (1976) pages 99-109. More preferred X_6 groups are Cl, Br, OCH_2CH_3, $OC(O)CH_3$, $OC(O)CF_3$,O-C(O)-OCH_2CH_3, O-C(O)-$OCH_2CH(CH_3)_2$, or O-C(O)-OCH_2-C_6H_5 in the presence of a non-nucleophilic base.



Formula (8)

Alternatively, the ester moiety of a compound of Formula 9



Formula (9)

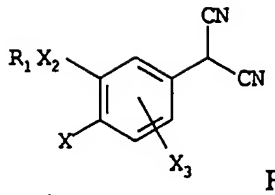
may be hydrolyzed to give the free acid, followed by activation of the acid moiety by a halogenating agent, such as an acid halide, oxalyl chloride, or phosphorous oxylchloride, etc. or a mixed anhydride and reaction with ammonia, an optionally substituted amine, optionally substituted hydroxylamine, or an optionally substituted hydrazine, produces the compounds of Formula (1) wherein R_{20} is -NR_7R_8, -NR_7-NR_7R_8, -NR_7OH, -NR_5OR_5, -$NR_5NR_5R_8$, -$NR_5(CH_2)_qR_8$;

b) or hydrolyzing a compound of Formula (9) as described above, to yield a compound of Formula (9) wherein R is H, and reacting it with ammonia, an optionally substituted amine, optionally substituted hydroxylamine, or an optionally substituted hydrazine and a compound of the formula $R_{28}N{=}C{=}NR_{28}$ wherein R_{28} is independently selected from alkyl; cycloalkyl, such as cyclohexyl or dicyclohexyl; alkyl (mono-or dialkyl amino), such as EDAC; aryl or arylalkyl, to produce the compounds of Formula (1) wherein R_{20} is an amine or substituted amine derivative; or

c) for compounds wherein R_3 is not H, or CH_2NH_2 and X and X_3 are substituted with other than Br, I, amino, formylamine, and NO_2, compounds of Formula (6) wherein X_5 is CN, derived by reaction of a compound of the Formula (6) wherein X_5 is halide, with e.g., sodium cyanide in DMF, are allowed to react with a strong hindered base, such as lithium diisopropylamide (LDA) or hexamethyldisilazylithium (LiHMDS) followed by reaction with, e.g., methyl or t-butyl bromo acetate to provide compounds of Formula (4) wherein R_3 is CN and R_{17} is H and R_{27} is CH_3 or t-butyl; conversion of such a Formula (4) compound to a Formula (4) compound wherein OR_{27} is NH_2 is accomplished as described above. Selective reduction of such a Formula (4) compound to a compound of the Formula (5) wherein R_3 is CN and R_{18} and R_{19} are H may be accomplished using, e.g., sodium bis(2-methoxyethoxy)aluminum hydride or by the method of Y. Mahi et al, Chem. Ind., 1976, 322. Further elaboration of such a compound of Formula (5) wherein R_{19} is H to a compound of Formula (5) wherein R_{19} is other than H, and then to a compound of Formula (1), may be accomplished as described above.

d) Compounds of the Formula (a) or Formula (5) wherein R_3 and R_{18} is alkyl or fluoro substituted alkyl may be derived from the corresponding Formula (1) or Formula (5) compound containing an oxo carbon species by deoxygenation or DAST treatment.

e) compounds wherein both R_3 and R_{18} are cyano are prepared in an analogous manner using a compound of Formula (10)



Formula (10)

and reacting with a base or a metal hydride followed by treatment with an appropriately substituted halo alkyl acetate to produce the compound of Formula (4) wherein both R_3 and R_{18} are CN; this may be elaborated as described above for other compounds of Formula (4) to produce a compound of Formula (1).

f) compounds of Formula (1) wherein X or X_3 are is formyl amine are formed at the last step, by formylating a compound wherein X or X_3 is NH_2, obtained by removal of a protecting group from the amine functionality. Such protective groups are well known to those skilled in the art, See Greene, T., supra.

g) compounds of Formula (1) wherein X or X_3 are Br or I may be prepared on a deprotected amine, diazotization of the amine, and diazonium displacement.

h) compounds of Formula (1) wherein X or X_3 are NO_2 may be prepared on a deprotected amine by oxidation of the amine to the nitro group.

i) compound of Formula (1) wherein R_3, R_{18}, R_{24}, R_{25} and R_{26} are other than hydrogen can readily be prepared by one skilled in the art using the techniques illustrated above.

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in standard manner for the treatment of the indicated diseases, for example orally, parenterally, sublingually, transdermally, rectally, via inhalation or via buccal administration. Those of skill in the formulation arts will be capable of preparing appropriate formulations targeted to one or more of these routes of administration.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

Each dosage unit for oral administration contains suitably from 0.001 mg to 100 mg/Kg, and preferably from .01 mg to 30 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.001 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt therof calculated as the free base. Each dosage unit for intranasal administration or oral inhalation contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 001 to 1.0% of a compound of Formula (I). Each dosage unit for rectal administration contains suitably 0.01 mg to 100 mg of a compound of Formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for parenteral administration is suitably abut 0.001 mg/Kg to 40 mg/Kg, for example abut 0.001 mg/Kg to 40 mg/Kg, of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 1200 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit antiinflammatory activity, or if used as a TNF inhibitor, the active ingredient is administered in an amount sufficient to inhibit TNF production such that normal or subnormal levels are achieved which are sufficient to ameliorate or prevent the disease state.

The biological activity of the compounds of Formula I as in PDE IV inhibitors are demonstrated by the following tests.

Inhibitory Effect of Compounds of Formula I on PDE IV

I. Isolation of PDE Isozymes

Phosphodiesterase inhibitory activity and selectivity of compounds is determined using a battery of five distinct PDE isozymes. The characteristics of these PDEs appear in Table 1. The tissues used as sources of the different isozymes are as follows: 1) PDE Ia, canine trachealis; 2) PDE Ib, porcine aorta; 3) PDE Ic, guinea-pig heart; 4) PDE III, guinea-pig heart; and 5) PDE IV, human monocyte. PDEs Ia, Ib, Ic and III are partially purified using standard chromatographic techniques (Torphy and Cieslinski, Mol. Pharmacol. 37:206-214, 1990). PDE IV is purified to kinetic homogeneity by the sequential use of anion-exchange followed by heparin-Sepharose chromatography (Torphy et al., J. Biol. Chem., 267: 1798-1804 (1992)).

TABLE 1. Characteristics of PDE isozymes.[a]

Peak	Isozyme	K_m (mM)	
		cAMP	cGMP
1a	cGMP-specific	135	4
Ib	Ca^{2+}/calmodulin-stimulated	50	5
Ic	Ca^{2+}/calmodulin-stimulated	1	2
III	cGMP-inhibited	0.4	8
IV	Ro 20-1724-inhibited	4	38

[a] Data are from Torphy and Cieslinski, supra.

[b] Nomenclature is from Beavo, Adv. Second Messenger Phosphoprotein Res. 22:1-38, 1988.

II. PDE Assay

Phosphodiesterase activity is assayed as described in Torphy and Cieslinski, Mol. Pharmacol. 37:206-214, 1990. IC_{50}s for compounds of this invention range from 25 nM to 500 mM.

III. cAMP Accumulation in U-937 Cells

The ability of selected PDE IV inhibitors to increase cAMP accumulation in intact tissues is assessed using U-937 cells, a human monocyte cell line that has been shown to contain a large amount of PDE IV. To assess the activity of PDE IV inhibition in intact cells, nondifferentiated U-937 cells (approximately 10^5 cells/reaction tube) were incubated with various concentrations (0.01-100 mM) of PDE inhibitors for one minute and 1 mM prostaglandin E2 for an additional four minutes. Five minutes after initiating the reaction, cells were lysed by the addition of 1M potassium carbonate and cAMP content was assessed by RIA. A general protocol for this assay is described in Brooker et al., Radioimmunassay of cyclic AMP and cyclic GMP, Adv. Cyclic Nucleotide Res., 10:1-33, 1979. Data are expressed as both an EC_{50} for increases in cAMP accumulation as a percentage of the maximum response to rolipram produced by 10 mM of the test compounds. EC_{50}s for compounds of this invention range from 0.3 mM to > 10 mM.

Inhibitory Effect of Compounds of Formula (I) on TNF Production

I. Inhibitory Effect of compounds of the Formula (I) on in vitro TNF production by Human Monocytes.

The inhibitory effect of compounds of the Formula (I) on in vitro TNF production by Human Monocytes may be determined by the protocol as described in Badger et al., EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

II. In vivo actity

Two models of endotoxin shock have been utilized to determine in vivo TNF activity for the compounds of the Formula (I). The protocol used in these models is described in Badger et al., EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The following exampled illustrate this invention but are not intended in any way to limit the scope of the invention. Reference is made to the claims for what is reserved to the inventors hereunder.

EXAMPLE 1

3-Cyclopentyloxy-4-methoxybenzaldehyde

3-Cyclopentyloxy-4-methoxybenzaldehyde A mixture of 3-hydroxy-4-methoxybenzaldehyde (40 g, 0.26 mol), potassium carbonate (40 g, 0.29 mol) and bromocyclopentane (32 mL, 0.31 mol) in dimethylformamide (0.25 L) was heated under an argon atmosphere at 100°C. After 4h, additional bromocyclopentane (8.5 mL, 0.08 mol) was added and heating was continued for 4h. The mixture was allowed to cool and was filtered. The filtrate was concentrated under reduced pressure and the residue was partitioned between ether and aqueous sodium bicarbonate. The organic extract was washed with aqueous sodium carbonate and was dried (potassium carbonate). The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with 2:1 hexanes/ether, to provide a pale yellow oil.

Analysis Calc. for $C_{13}H_{16}O_3$: C 70.89, H 7.32; found: C 70.71, H 7.33.

EXAMPLE 2

N-[3-(3-Cyclopentyloxy-4-methoxyphenyl)propyl]oxamide

2a. 3-(3-Cyclopentyloxy-4-methoxyphenyl)prop-2-enoic acid A mixture of 3-cyclopentyloxy-4-methoxybenzaldehyde (4.4 g, 20 mmol), malonic acid (4.16 g, 40 mmol) and piperidine (0.3 mL) in pyridine (8 mL) under an argon atmosphere was heated at 80°C for 4h. The mixture was cooled, the residue was poured into ice water and was acidified with concentrated hydrochloric acid (10 mL). The solid was collected by filtration, was washed well with acidic water and was dried.

2b. 3-(3-Cyclopentyloxy-4-methoxyphenyl)prop-2-enamide To a solution of 3-(3-cyclopentyloxy-4-methoxyphenyl)prop-2-enoic acid (0.3 g, 1.14 mmol) in chloroform (5.2 mL) under an argon atmosphere was added triethylamine (0.16 mL, 1.14 mmol). The solution was cooled to 0°C and ethyl chloroformate (0.11 mL, 1.14 mmol) was added. The resulting mixture was stirred at 0°C for 20 min. Ammonia was bubbled into the solution, the solution was allowed to warm to room temperature, was stirred for 1h and was allowed to stand overnight. The mixture was partitioned between methylene chloride and water, the organic extract was dried (potassium carbonate) and was concentrated under reduced pressure to provide a solid.

2c. 3-(3-Cyclopentyloxy-4-methoxyphenyl)propanamide A solution of 3-(3-cyclopentyloxy-4-methoxyphenyl)prop-2-enamide (0.215 g, 0.82 mmol) and 10% palladium on carbon (0.2 g) in methanol (10 mL) was hydrogenated at 50 psi for 1.5h. The mixture was filtered through Celite, the filtrate was evaporated and was partitioned between methylene chloride and water. The organic layer was dried (potassium carbonate) and was evaporated to a solid.

2d. 3-(3-Cyclopentyloxy-4-methoxyphenyl)propylamine To a suspension of lithium aluminum hydride (0.043 g, 1.13 mmol) in ether (10 mL) at room temperature under an argon atmosphere was added dropwise a solution of 3-(3-cyclopentyloxy-4-

methoxyphenyl)propanamide (0.19 g, 0.71 mmol) in tetrahydrofuran/ether. The resulting mixture was heated at reflux for 2h and then stirred at room temperature overnight. The reaction mixture was quenched by the successive dropwise addition of water (0.043 mL), 15% sodium hydroxide (0.043 mL) and water (0.13 mL). The mixture was filtered and was diluted with methylene chloride, the filtrate was washed with water and was dried (potassium carbonate). Removal of the solvent *in vacuo* provided the amine.

2e. Methyl N-[3-(3-cyclopentyloxy-4-methoxyphenyl)propyl]oxamate A solution of 3-(3-cyclopentyloxy-4-methoxyphenyl)propylamine (0.14 g, 0.57 mmol) in tetrahydrofuran (2 mL) was cooled to 0°C and was treated with triethylamine (0.09 mL, 0.57 mmol) and methyl oxalyl chloride (0.065 mL, 0.57 mmol). The reaction was stirred under an argon atmosphere for 0.5h, then partitioned between acidic water and methylene chloride. The extract was dried (potassium carbonate) and was evaporated.

2f. N-[3-(3-Cyclopentyloxy-4-methoxyphenyl)propyl]oxamide A solution of methyl N-[3-(3-cyclopentyloxy-4-methoxyphenyl)propyl]oxamate (0.18 g, 0.54 mmol) in methanol (2 mL) in a pressure vessel was cooled to -78°C and ammonia (2 mL) was condensed into the vessel. The vessel was sealed, was allowed to come to room temperature and was stirred overnight. The ammonia was evaporated, the residue was dissolved in chloroform, the solution was washed with water and was dried (potassium carbonate). The resultant solid was triturated with ether/methylene chloride, was filtered and was dried : m. p. 163°C.

Analysis Calc. for $C_{17}H_{24}N_2O_4 \cdot 1/8\ H_2O$: C 63.29, H 7.58, N 8.61; found: C 63.16, H 7.34, N 8.75.

EXAMPLE 3

Methyl N-[3-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)propyl]oxamate

3a. 4-Difluoromethoxy-3-hydroxybenzaldehyde A vigorously stirred mixture of 3,4-dihydroxybenzaldehyde (50 g, 362 mmol) and potassium carbonate (50 g, 362 mol) in dimethylformamide (250 mL) was heated under an atmosphere of chlorodifluoromethane using a -78°C condenser at 100°C for 5.5h. An additional quantity of potassium carbonate (10 g) was added and the reaction was continued for another 0.5h. The mixture was allowed to cool, was acidified to pH 5-6 with concentrated hydrochloric acid and was concentrated under reduced pressure. The residue was partitioned between ether and 3N aqueous hydrochloric acid and was extracted five times with ether. The organic extract was dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography, eluting with 2:1 hexanes/ethyl acetate, to provide a yellow solid, which was triturated with ethyl acetate/hexanes to provide, in three crops, a white solid: m.p. 84-86°C.

3b. 3-Cyclopropylmethoxy-4-difluoromethoxybenzaldehyde To a mixture of 3-hydroxy-4-difluoromethoxybenzaldehyde (19.55 g, 104 mmol) and potassium carbonate (21.56 g, 156 mmol) in dimethylformamide (150 mL) under an argon atmosphere at 60°C was added bromomethylcyclopropane (15.13 mL, 156 mmol) and the mixture was stirred and heated at

65°C. After 1.5h, the mixture was allowed to cool and was filtered. The filtrate was concentrated under reduced pressure, water was added and the mixture was extracted four times with ethyl acetate. The organic extract was washed twice with water and was dried (sodium sulfate). The solvent was removed *in vacuo* to provide an oil.

3e. 3-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)prop-2-enoic acid A mixture of 3-cyclopropylmethoxy-4-difluoromethoxybenzaldehyde (0.4 g, 1.65 mmol), malonic acid (0.34 g, 3.3 mmol) and piperdine (10 drops) in pyridine (0.66 mL) under an argon atmosphere was heated at 80°C for 4.5h. The mixture was cooled, the residue was acidified with 3N hydrochloric acid, the solid was collected by filtration, was washed well with 3N hydrochloric acid and was dried: m.p. 161-163°C.

3f. 3-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)prop-2-enamide To a solution of 3-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)prop-2-enoic acid (0.55 g, 1.93 mmol) in chloroform (10 mL) under an argon atmosphere was added triethylamine (0.27 mL, 1.93 mmol). The solution was cooled to 0°C and ethyl chloroformate (0.18 mL, 1.93 mmol) was added. The resulting mixture was stirred at 0°C for 15 min. Ammonia was bubbled into the solution, the solution was allowed to warm to room temperature and was stirred for 3 days. The mixture was partitioned between ethyl acetate and acidic brine, was extracted twice, the organic extract was washed with acidic brine, was dried (magnesium sulfate) and was concentrated under reduced pressure. Purification by flash chromatography, eluting with 10-20% methanol/methylene chloride, provided a solid: m.p. 134-136°C.

3g. 3-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)propanamide A solution of 3-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)prop-2-enamide (0.36 g, 1.27 mmol) and 10% palladium on carbon in methanol (20 mL) was hydrogenated at 50 psi for 1.5h. The mixture was filtered through Celite, the filtrate was evaporated and the residue was redissolved, was filtered through a short pad of silica gel and was evaporated to a solid: m.p. 103-105°C.

3h. 3-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)propyl-amine. To a suspension of lithium aluminum hydride (0.066 g, 1.74 mmol) in ether (20 mL) at room temperature under an argon atmosphere was added dropwise a solution of 3-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)propanamide (0.31 g, 1.09 mmol) in tetrahydro-furan/ether (10 mL). The resulting mixture was heated at reflux for 2h and then was stirred at room temperature overnight. The reaction mixture was quenched by the successive dropwise addition of ethyl acetate and then aqueous sodium potassium tartrate, was poured into brine and was extracted twice with methylene chloride. The organic extract was dried (potassium carbonate) and the solvent was revoved *in vacuo* to provide the amine.

3i. Methyl N-[3-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)propyl]oxamate A solution of 3-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)propylamine (0.31 g, 1.14 mmol) in tetrahydrofuran (20 mL) was cooled to 0°C and was treated with triethylamine (0.18 mL, 1.25 mmol) and methyl oxalyl chloride (0.11 mL, 1.14 mmol). The reaction was

stirred under an argon atmosphere for 0.5 h, was partitioned between acidic water and methylene chloride and was extracted twice. The organic extract was dried (magnesium sulfate) and evaporated. Purifi-cation by flash chromatography, eluting with 1:1 hexanes/ethyl acetate, provided a tan solid: m.p. 33-35°C.

Analysis Calc. for $C_{17}H_{21}F_2NO_5$: C 57.14, H 5.92, N 3.92; found: C 57.39, H 6.00, N 3.90.

EXAMPLE 4

N-[3-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)propylloxamide

N-[3-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-propylloxamide A solution of methyl N-[3-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)propyl]-oxamate (0.1 g, 0.28 mmol) in methanol (3 mL) was cooled to -78°C and ammonia (2 mL) was condensed into the vessel. The the mixture was allowed to come to room temperature and the ammonia was evaporated under a stream of argon. The residue was partitioned between methylene chloride and brine, was extracted twice with methylene chloride, the organic extract was dried (magnesium sulfate) and was evaporated. The solid product was precipitated from ethyl acetate with hexane: m. p. 151-152°C.

Analysis Calc. for $C_{16}H_{20}F_2N_2O_4$: C 56.14, H 5.89, N 8.18; found: C 56.22, H 5.85, N 8.08.

EXAMPLE 5

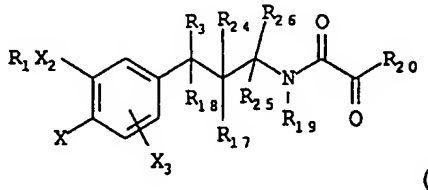
N-[3-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)propylloxamic acid

N-[3-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-propylloxamic acid To a solution of methyl N-[3-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)propyl]-oxamate (0.05 g, 0.14 mmol) in 5:5:2 tetrahydrofuran/methanol/water (2 mL) at room temperature under an argon atmosphere was added powdered sodium hydroxide (0.02 g, 0.42 mmol). After 3h, the mixture was acidified with 3N hydrochloric acid, was extracted three times with methylene chloride, the organic extract was dried (magnesium sulfate) and was evaporated to a tan solid: m.p. 134-135°C.

Analysis Calc. for $C_{16}H_{19}F_2NO_5$: C 55.97, H 5.58, N 4.08; found: C 55.81, H 5.69, N 3.95.

CLAIMS:

1. This invention comprises oxamides of Formula (I)



(I)

or a pharmaceutically acceptable salt thereof;

wherein

R_1 is C_{1-12} alkyl unsubstituted or substituted by 1 or more halogens, C_{3-6} cyclic alkyl unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group, C_{4-6} cycloalkyl containing one or two unsaturated bonds, C_{7-11} polycycloalkyl, $(CR_{14}R_{14})_nC(O)$-O-$(CR_{14}R_{14})_m$-R_{10}, -$(CR_{14}R_{14})_nC(O)$-O-$(CR_{14}R_{14})_r$-R_{11}, -$(CR_{14}R_{14})_xOH$, -$(CR_{14}R_{14})_sO(CR_{14}R_{14})_m$-$R_{10}$, -$(CR_{14}R_{14})_sO(CR_{14}R_{14})_r$-$R_{11}$, -$(CR_{14}R_{14})_n$-$(C(O)NR_{14})$-$(CR_{14}R_{14})_m$-$R_{10}$, -$(CR_{14}R_{14})_n$ -$(C(O)NR_{14})$-$(CR_{14}R_{14})_r$-R_{11}, -$(CR_{14}R_{14})_y$-R_{11}, or -$(CR_{14}R_{14})_z$-R_{10};

X is YR_2, halogen, nitro, $NR_{14}R_{14}$, or formamide;

X_2 is O or NR_{14};

X_3 is hydrogen or X;

Y is O or $S(O)_m$;

R_2 is -CH_3 or -CH_2CH_3, each may be unsubstituted or substituted by 1 to 5 fluorines;

R_3 is hydrogen, halogen, CN, C_{1-4}alkyl, halo-substituted C_{1-4}alkyl, cyclopropyl unsubstituted or substituted by R_9, -OR_5, -CH_2OR_5, -NR_5R_{16}, -$CH_2NR_5R_{16}$, -$C(O)OR_5$, -$C(O)NR_5R_{16}$, -$CH=CR_9R_9$, -$C\equiv CR_9$ or -C(Z)H;

R_4 is independently hydrogen, Br, F, Cl, -NR_5R_{16}, NR_6R_{16}, -NO_2, -$C(Z)R_7$, -$S(O)_mR_{12}$, -CN, OR_5, -$OC(O)NR_5R_{16}$, (1 or 1-(R_5)-2-imidazolyl), -$C(NR_{16})NR_5R_{16}$, -$C(NR_5)SR_{12}$, -$OC(O)R_5$, -$C(NCN)NR_5R_{16}$, -$C(S)NR_5R_{16}$, $N(R_{16})C(O)R_{15}$, oxazolyl, thiazolyl, pyrazolyl, triazolyl or tetrazolyl, or when R_5 and R_{16} are NR_5R_{16} they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S;

R_5 is independently hydrogen or C_{1-4}alkyl, unsubstituted or substituted by one to three fluorines;

R_6 is R_5, -$C(O)R_5$, -$C(O)C(O)R_7$, -$C(O)NR_5R_{16}$, -$S(O)_mR_{12}$, -$C(NCN)SR_{12}$, -$C(NCN)R_{12}$, -$C(NR_{16})R_{12}$, -$C(NR_{16})SR_{12}$, or -$C(NCN)NR_5R_{16}$;

R_7 is OR_5, -NR_5R_{16}, or R_{12};

R_8 is hydrogen or A;

R_9 is hydrogen, F or R_{12};

R_{10} is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC_{1-3}alkyl, halo substituted arlyoxyC_{1-3}alkyl, indanyl, indenyl, C_{7-11} polycyclo-alkyl, furanyl, pyranyl, thienyl, thiopyranyl, (3- or 4-tetrahydropyranyl), (3- or 4-tetrahydrothiopyranyl), 3-tetrahydrofuranyl, 3-tetrahydrothienyl, C_{3-6} cylcoalkyl, or a C_{4-6}cycloalkyl containing one or two unsaturated bonds, wherein the cylcoalkyl and heterocyclic moieties may be unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

R_{11} is 2-tetrahydropyranyl or 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl or 2-tetrahydrothienyl unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

R_{12} is C_{1-4}alkyl unsubstituted or substituted by one to three fluorines;

R_{14} is independently hydrogen or a C_{1-2}alkyl unsubstituted or substituted by fluorine;

R_{15} is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, or pyrrolyl, and each of the heterocyclics may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{16} is OR_5 or R_5, or when R_5 and R_{16} are NR_5R_6 they may, together with the nitrogen, form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N, or S;

R_{17} and R_{26} are independently hydrogen, halogen, C_{1-4}alkyl, halo-substituted C_{1-4}alkyl, cyclopropyl unsubstituted or substituted by R_9, $-CH_2OR_5$, $-CH_2NR_5R_{16}$, $-C(O)OR_5$, $-C(O)NR_5R_{16}$ or -C(Z)H;

R_{18}, R_{24} and R_{25} are independently hydrogen, F, CN, and C_{1-4} alkyl optionally substituted by one or more fluorines; or

R_3 and R_{18} together can form a (=O) keto or cyclopropyl moiety;

provided that when R_3 is OH then R_{18} is hydrogen or CH_3;

R_{19} is hydrogen, $-(CH_2)_mA$, or $-CH_2O(CH)_mA$;

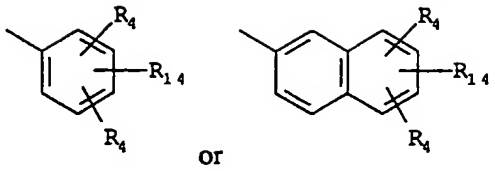
R_{20} is $-O(CH_2)_qR_8$, $-NR_5OR_5$, $-NR_5NR_5R_8$, $-NR_5(CH_2)_qR_8$, $-OCH_2NR_5C(O)R_{21}$, $-OCH_2C(O)NR_{22}R_{23}$, $-OCH(R_5)OC(O)$, C_{1-4}alkyl, $-OCH(R_5)C(O)OC_{1-3}$alkyl;

R_{21} is CH_3 or phenyl;

R_{22} is hydrogen, CH_3, CH_2CH_3, or CH_2CH_2OH;

R_{23} is hydrogen, CH_3, CH_2CH_3, CH_2CH_2OH, or CH_2CONH_2;

A is C_{1-6}alkyl (2-, 3-, or 4-pyridyl), 4-morpholinyl, 4-piperidinyl, (1-, 2-, 4- or 5-imidazolyl), (2- or 3-thienyl), (2- or 5-pyrimidyl), (4 or 5-thiazolyl), triazolyl or quinolinyl, all of which may be unsubstituted or substituted by one or more R_4 groups; or A is $-(CH_2)_rSR_{12}$; or A is a formula of (a) or (b)



or

(a) (b)

where the R_4 and R_{14} groups on the naphtyl ring may be substituted at any open position;

Z is O, NR_{12}, NOR_5, NCN, $C(\text{-}CN)_2$, CR_5NO_2, $CR_5C(O)OR_5$, $CR_5C(O)NR_5R_5$, $\text{-}C(\text{-}CN)NO_2$, $C(\text{-}CN)C(O)OR_{12}$ or $C(\text{-}CN)C(O)NR_5R_5$;

m is 0 to 2;

n is 1 to 4;

q is 0 to 1;

r is 1 to 2;

s is 2 to 4;

x is 2 to 6;

y is 1 to 6;

z is 0 to 6;

provided that:

m is 2 when R_{10} is OH in $(CR_{14}R_{14})_n\text{-}C(O)O\text{-}(CR_{14}R_{14})_m\text{-}R_{10}$, $(CR_{14}R_{14})_n\text{-}(C(O)NR_{14})\text{-}(CR_{14}R_{14})_m\text{-}R_{10}$, or $C(R_{14}R_{14})_sO(CR_{14}R_{14})_mR_{10}$; and further provided that

when A is N-morpholinyl, N-piperidinyl, N-imidazolyl or N-triazolyl, then q is not 1; and

Z is 2-6 in $\text{-}C(R_{14}R_{14})_zR_{10}$ when R_{10} is OH.

2. A compound of claim 1 wherein R_1 is CH_2-cyclopropyl, $CH_2\text{-}C_{5\text{-}6}$ cycloalkyl, $C_{4\text{-}6}$ cycloalkyl, phenyl, tetrahydrofuran-3-yl, 3- or 4-cyclopentenyl, $\text{-}C_{1\text{-}2}$alkyl optionally substituted by one or more fluorines, $\text{-}(CH_2)_nC(O)\text{-}O\text{-}(CH_2)_mCH_3$, $\text{-}(CH_2)_sO(CH_2)_m\text{-}CH_3$ or $\text{-}(CH_2)_{2\text{-}4}OH$; X_2 is oxygen; X_3 is hydrogen; X is YR_2 and Y is O; R_2 is a $C_{1\text{-}2}$alkyl optionally substituted by one or more fluorines; R_3 is hydrogen, $C{\equiv}CR_9$, CN, C(O)H, CH_2OH, CH_2F, CF_2H, or CF_3; R_{18} is hydrogen, CN or $C_{1\text{-}4}$alkyl optionally substituted by one or more fluorines; R_{19} is hydrogen or $(CH_2)_mA$; R_{20} is $O(CH_2)_qR_8$, NR_5OR_5 or $NR_5(CH_2)_qR_8$.

3. A compound of claim 2 wherein R_1 is $C_{1\text{-}2}$ alkyl substituted by 1 or more fluorines, CH_2-cyclopropyl, CH_2-cyclopentyl, cyclopentyl or cyclopentenyl; R_2 is methyl or fluoro substituted $C_{1\text{-}2}$ alkyl; R_3 is hydrogen, $C{\equiv}CH$ or CN; and A is 2-, 3- or 4-pyridyl, 4-morpholinyl, 2-thienyl, 2-imidazole or 4-thiazolyl, each of which may be substituted or unsubstituted by NR_5R_{16} or $NR_5C(O)R_5$; R_{20} is OR_5, NR_5OR_5 or $NHCH_2A$.

4. A compound of claim 3 wherein R_1 is cyclopentyl, CF_3, CH_2F, CHF_2, CF_2CHF_2, CH_2CF_3, CH_2CHF_2, CH_3, CH_2-cyclopentyl, CH_2-cyclopropyl or cyclopentenyl; R_2 is CH_3, CF_3, CHF_2, or CH_2CHF_2; one R_3 is hydrogen and the other R_3 is hydrogen, $C{\equiv}CH$ or CN and is in the 4-position.

5. A compound of claim 1 selected from the group consisting of:
N-[3-(3-cyclopentyloxy-4-methoxyphenyl)propyl]oxamide;
methyl N-[3-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)propyl]oxamate;
N-[3-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)propyl]oxamide; and
N-[3-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)propyl]oxamic acid.

6. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

7. A method of treatment of allergic and inflammatory diseases which comprise administering to a subject in need thereof an effective amount of a compound of claim 5.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/00557

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07C 237/22; A61K 31/16
US CL :564/158; 514/616.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 564/158; 514/616

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A, 92/00968 (Bender et al.) 23 January 1992, see entire document.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
18 MARCH 1993	05 APR 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer SCOTT RAND Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/00557

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains claims which do not relate to one invention so as to form a single inventive concept. Thus,there is lack of unity under PCT Rule 13.

Compounds, compositions, and method of treating allergy or inflammation wherein the species comprises.

I. Oxamate compounds, such as Example 3, classified in class 560/39 and 514/563, for example (claims 1-7, in part).

II. Oxamic acid compounds, such as Example 5, classified in class 562/444 and 514/563, for example (claims 1-7 in part).

III. Oxamides, such as Examples 2 and 4, classified in Class 564/158 and 514/616, for example (claims 1-7, in part).

Groups I-III do not fulfill the requirement for unity of invention under Rule 13.2 the various species are so diverse so as to lack a special technical feature in common.